AD-A262 196

REPORT DOCUMENTATION PAGE

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE 17 March 1993	3. REPORT TYPE AND DATES COVERED Technical Report

4. TITLE AND SUBTITLE
Chiral Host-Guest Recognition in the Solvent Free Gas Phase as Determined by Fourier Transform Ion Cyclotron Resonance Mass Spectrometry (FT-ICR/MS)

5. FUNDING NUMBERS
N00014-91-J-1710
R & T Code 413p002

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8. PERFORMING ORGANIZATION REPORT NUMBER

Technical Report No. 17

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800 North Quincy Street
Arlington, VA 22217-5000

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

N/A

DTIC
ELECTE
MAR 3 0 1993
S E D

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION/AVAILABILITY STATEMENT

Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 words)

Chiral recognition is observed for a gas-phase host-guest system by using Fourier transform ion cyclotron resonance mass spectrometry to determine equilibrium constants for the transfer of R-or S-(1-naphthyl)ethylammonium ($NapEt^+$) cation from S,S-dimethyl-diketopyridino-18-crown-6 to unsubstituted 18-crown-6. The unsubstituted crown has substantially higher affinity for both guests than the chiral crown. The measured equilibrium constants are 130 ± 15 for R-$NapEt^+$, and 567 ± 68 for S-NapEt+, yielding a difference of 4.2 ± 0.4 kJ mol^{-1} between the stabilities of the complexes of the two enantiomeric guests with the chiral host.

93 3 29 051

93-06395

14. SUBJECT TERMS

16. PRICE CODE
N/A

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	UL

OFFICE OF NAVAL RESEARCH

Grant N00014-91-J-1710

R&T Code 413p002

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Chiral Host-Guest Recognition in the Solvent Free Gas Phase as Determined by Fourier Transform
Ion Cyclotron Resonance Mass Spectrometry (FT-ICR/MS)

by

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Several groups have reported the use of fast atom bombardment mass spectrometry (FAB-MS) to examine chiral recognition.[1,2] In general, the experiments involved measurement of the relative intensities of adduct peaks arising from interactions between chiral molecules in a FAB ion source. In several cases, recognition was observed. However, conditions in the FAB source make it difficult to distinguish whether adduct formation took place in the gas phase or prior to desorption from the FAB matrix, so it is unclear whether the results reflect recognition in the gas phase or in solution.

Our experiments involve measurement of equilibrium constants for reactions involving transfer of the R and S enantiomers of α-(1-naphthyl)ethylammonium (NapEt$^+$) cation between S,S-dimethyldiketopyridino-18-crown-6 (S,S-1) and the achiral host 18-crown-6 (18C6) (Reaction 1). The experimental procedure has been described.[3,4] In a typical experiment, 18-crown-6 and the chiral host and one of the amines were introduced into the instrument via temperature-controlled solid probes. Absolute pressures in the trapping cell were typically about 5-10 x 10^{-8} Torr. Ions were formed using 70 eV electron impact, and after approximately 3 seconds reaction time, the only ions observed in the trapping cell were the complexes of NapEt$^+$ with the two host molecules. The time scale of these reactions is long enough that we can safely assume thermalization of the ions. Reaction (1) was monitored as a function of time until the S,S-1•NapEt$^+$/18C6•NapEt$^+$ ratio became constant. Ejection of either equilibrium product ion results (after suitable delay) in re-establishment of the same reactant/product ratio, verifying the existence of true equilibrium condition. Equilibrium constants K were measured by application of equation (2).

$$K = \frac{I_{18C6 \cdot NapEt^+} \cdot P_{S,S-1}}{I_{S,S-1 \cdot NapEt^+} \cdot P_{18C6}} \tag{2}$$

The reactant and product ion intensities at equilibrium, $I_{18C6 \cdot NapEt^+}$ and $I_{S,S-1 \cdot NapEt^+}$, were read

directly from the mass spectra. The relative pressures of neutral S,S-1 and 18C6, $P_{S,S-1}$ and P_{18C6}, were determined by measuring the relative rates of proton attachment to each species at short reaction times, with the assumption that the efficiency of proton attachment for the two ligands is identical.

Mean equilibrium constants for reaction (1) involving the two enantiomeric guests, as well as the ΔG values derived from them using an estimated cell temperature of 350 K, are given in Table 1. 18C6 has a considerably higher intrinsic affinity for both guests than does S,S-1, probably reflecting the greater flexibility of the former ligand which enables it to more easily adopt conformation favorable for binding the guest.
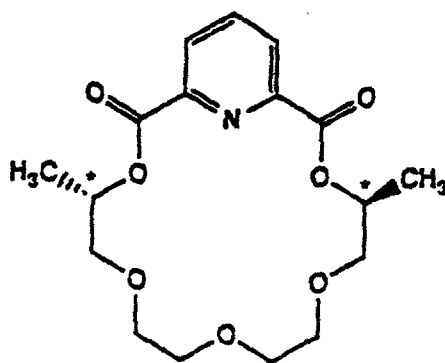
The values of K for S-NapEt$^+$ is greater than that for R-NapEt$^+$ by more than a factor of 4, corresponding to the S,S-1·S-NapEt$^+$ complex. Thus, this system exhibits considerable chiral recognition, which is easily measured using FT-ICR/MS techniques.

The S,S-1-NapEt$^+$ system also exhibits chiral recognition in condensed media. When crystals were formed from 1 equivalent of S,S-1 mixed with 2 equivalents of racemic NapEt$^+$, NMR analysis found the resulting complexes contained 68% of the R enantiomer and 32% of the S enantiomer of NapEt$^+$.[5] From the difference between the complex formation constants measured in methanol[5] using titration calorimetry, it can be determined that the R-NapEt$^+$ complex is 2.3 kJ mol^{-1} more stable than that of S-NapEt$^+$ with S,S-1, qualitatively in excellent agreement with the gas phase result.
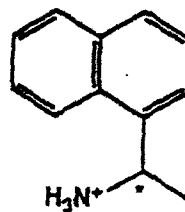
The gas phase results are of particular value because they can be directly compared with the predictions of theory. Molecular mechanics calculations indicate that this system should exhibit recognition in the gas phase. In a thorough search of configuration space, a value of 2.9 kJ mol^{-1} was obtained for the difference in free energies of activation for complex dissociation, $(\Delta\Delta G\ddagger)$.[6] Our own much more limited calculations, using the MM+ version of MM2 implemented in the HyperChem™ program, give a difference of 1.8 kJ mol^{-1} between the lowest-energy conformations found for each enantiomer, although our search of configuration space was probably not sufficiently thorough to locate

the global minima. These values can be compared with a $\Delta\Delta G\ddagger$ value measured in CD_2Cl_2[5] of 4.6 kJ mol^{-1}, in close similarity to the gas phase stability difference.

In summary, ion-molecule reactivity using chiral reagents can be used to probe chirality in the gas phase. It is now feasible to distinguish enantiomeric structures using mass spectrometric methods. FT-ICR/MS is a powerful new tool for the study of molecular recognition under solvent-free conditions. Solvation has a small but measurable masking effect on the extent of recognition.
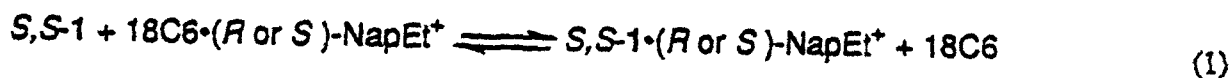

α-(1-naphthyl)ethylammonium
(NapEt[+])

1

$$S,S\text{-}1 + 18C6\bullet(R \text{ or } S)\text{-NapEt}^+ \rightleftharpoons S,S\text{-}1\bullet(R \text{ or } S)\text{-NapEt}^+ + 18C6 \tag{1}$$

Table 1. Mean equilibrium constants, K, with standard deviations, measured for transfer of S- or R-NapEt[+] from S,S-1 to 18C6 in the gas phase. ΔG values derived assuming a cell temperature of 350 K.

Guest	K	$\log K$	ΔG, kJ mol^{-1}
S-NapEt[+]	567 ± 68	2.75 ± 0.05	-18.4 ± 0.3
R-NapEt[+]	130 ± 15	2.11 ± 0.05	-14.2 ± 0.3

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